Examiner alleges that Applicants' specification is insufficient to have enabled one of skill in the art to make and/or use the claimed invention. Ultimately, the Examiner suggests that "[A]pplicants provide at least *in vitro* data that establishes the bacterial growth inhibitory efficacy that has been asserted." (Office Action dated June 12, 2002, page 10, lines 7-8.) Applicants respectfully traverse this rejection for at least the reasons of record and the additional reasons articulated below.

"A specification disclosure which contains a teaching of the manner and process of making and using an invention ... must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein... ." M.P.E.P § 2164.04 (emphasis supplied). To satisfy the Examiner's burden of supporting an enablement rejection, "specific technical reasons are always required". M.P.E.P. § 2164.04.

The Examiner disregards Applicants' arguments made previously of record, stating that "whether one would have reason to doubt the asserted utility ... is a moot issue, since no rejection under § 101 has been imposed." (Office Action dated June 12, 2002, page 3, lines 5-7.) And the Examiner opines that some structurally similar compounds *might not* exhibit the disclosed utility. Applicants respectfully submit, however, that this is insufficient to constitute a reasonable doubt. To the contrary, Applicants submit that "evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility." *In re Brana*, *supra*, n.2 at 1566, 34 U.S.P.Q.2d at 1442.

The Examiner must articulate a specific reason for doubting Applicants' asserted antibacterial activity. However, the Examiner merely states that "[t]he fact is that, where

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antibacterial activity is concerned, structure/activity relationships are unpredictable." (Office Action dated June 12, 2002, page 7, lines 13-14.) And, for support, the Examiner cites references that are not directly relevant to Applicants' asserted utility. (Office Action dated June 12, 2002, page 6, line 14 through page 7, line 9.) Thus, the Examiner has failed to back up his allegations "with acceptable evidence or reasoning" inconsistent with what Applicants assert in the specification. M.P.E.P. § 2164.04.

Applicants do not "merely suggest" or "predict" antibacterial activity of the claimed compounds and compositions. Applicants specifically assert such activity in the specification by providing that the claimed streptogramin derivatives can be used as antibacterials. (Specification, page 8, lines 12-19.) Applicants disclose that the claimed compounds and compositions are in fact useful by disclosing, for example, that "[i]n vivo, on experimental infections of mice with Staphylococcus aureus IP 8203 at doses of between 25 and 150 mg/kg orally and/or subcutaneously (CD_{50}), they synergize the antimicrobial activity of pristinamycin IB of pristinamycin I_A or of quinupristin (30/70 combination)." (Specification, page 11, lines 20-25.) For example, the specification also provides that "[n]one of the products exhibited toxicity at doses of 100 mg/kg or greater than 300 mg/kg by the subcutaneous route." (Specification, page 11, line 26 through page 12, line 2.) The disclosures set forth in Applicants' specification are objective truths, which are presumed true unless there is a reason to doubt them. The Examiner has not provided sufficient evidence to rebut Applicants' presumptively true specification.

Further, it is unclear how much trouble and expense the Examiner would have Applicants resort to in supporting their presumptively enabled and accurate specification

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with extrinsic evidence. For example, the Examiner provides that "*in vitro* data are not necessarily predictive of *in vivo* efficacy." (Office Action dated June 12, 2002, page 9, lines 11-12.) And the Examiner provides citations to references that allegedly provide that not all compounds active *in vitro* are also active *in vivo*. Clearly, this suggests that even if Applicants were to provide "*at least in vitro* data" in response to the Examiner's suggestion, Applicants would further be required to submit *in vivo* data. Applicants respectfully submit that the Examiner has imputed a far more tremendous burden on Applicants than is required by law, especially in light of the fact that the Examiner himself has not satisfied his burden of establishing a lack of enablement under 35 U.S.C. § 112, first paragraph, which is detailed in M.P.E.P. § 2164.

Unless and until the Examiner has established that one skilled in the art would reasonably doubt Applicants' asserted utility, Applicants are not required to provide evidence of testing or otherwise provide proof to support their asserted utility. *See* M.P.E.P. § 2164.05; *see also*, *In re Brana*, *supra*, n.2 at 1566, 34 U.S.P.Q.2d at 1441 (Fed. Cir. 1995) (The Office erred in requiring applicants "to substantiate their presumptively correct disclosure to avoid a rejection under 35 U.S.C. § 112, first paragraph" because the Office failed to satisfy its burden of showing that one would reasonably doubt applicants' asserted utility.)

As the Examiner has failed to establish a *prima facie* case of nonenablement, Applicants respectfully request withdrawal of the rejection under § 112, first paragraph.

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III. Rejections Under 35 U.S.C. § 112, Second Paragraph

Applicants acknowledge and appreciate that the rejection of claims 17-19 has been withdrawn. The Examiner, however, has maintained the rejection of claims 20-33 under 35 U.S.C. § 112, second paragraph, as indefinite for failing to point out and distinctly claim the subject matter that Applicants regard as the invention. (Office Action dated June 12, 2002, pages 10-13.)

If the scope of the invention can be determined from the language of the claims with a reasonable degree of certainty, then any rejection under 35 U.S.C. § 112, second paragraph, is improper. Applicants respectfully submit that their claims meet this statutory standard, and, thus, all rejections under § 112, second paragraph, should be withdrawn.

A. The Term "Deoxopristinamycin IIA" in Claims 20-24 Is Proper

The Examiner has rejected claims 20-24, alleging that the term "deoxopristinamycin IIA" may only be used if accompanied by a chemical name or structure. (Office Action dated June 12, 2002, page 10, lines 14-19.) Although Applicants disagree, Applicants have rendered moot this rejection by providing the chemical formulae for each of the streptogramin group A or group B derivatives recited in claims 20-24. Applicants respectfully request withdrawal of this rejection.

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B. The Examiner Has Improperly Analyzed the Definiteness of Claims 25 and 26 in a Vacuum

The Examiner has rejected claims 25 and 26 alleging that they encompass a "process in which the time and conditions are not effective to form a compound of formula I" and because the claims allegedly do not require isolation of the final product. (Office Action dated June 12, 2002, page 10, line 20 through page 12, line 18.) Applicants disagree and respectfully traverse this rejection for at least the reasons of record and the following reasons.

First, Applicants have amended claims 25 and 26 by inserting the phrase "for a time and under conditions to form a group A streptogramin derivative according to claim 17," as suggested by the Examiner. Thus, Applicants have rendered moot this ground for rejection.

Second, the Examiner alleges that, if the final product is never isolated, one cannot be in possession of the target compound. (Office Action dated June 12, 2002, page 11, lines 1-17.) But it appears that the Examiner is actually questioning how one would use the contents of his hypothetical flask, which he alleges would contain "unreacted starting materials, solvent, the 'target' compound, and other impurities." (Office Action dated June 12, 2002, page 11, lines 23-26.) Claims 25 and 26, however, are directed to processes for preparing group A streptogramin derivatives according to claim 17, and regardless of whether other materials are found in the flask proposed by the Examiner, Applicants' group A streptogramin derivatives according to claim 17 will also be present therein. Thus, contrary to the Examiner's allegations, if one were to perform the claimed processes, one would be in possession of such compounds.

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Applicants recite numerous specific examples in their specification that provide sufficient guidance to one skilled in the art to be able to practice the subject matter of claims 25 and 26. Additional limitations would only be required to distinguish over prior art, but in this case the Examiner has not asserted any such prior art. Additionally, Applicants note that 35 U.S.C. § 271(g), which recites that "[w]hoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer... ." Thus, very generally, to infringe a process claim one must practice each of the steps of such a process. Although one practicing Applicants' processes of claims 25 or 26 with an isolation step would still infringe those claims, one would not be required to perform an isolation step in order to infringe, e.g., preparation of the claimed group A streptogramin derivatives according to claim 17 without isolation would also infringe. Nonetheless, Applicants have added new claims 34 and 35, which each recite an isolation step. Thus, Applicants respectfully request withdrawal of this rejection.

C. **The Term "Group B Streptogramin Derivative" Is Sufficient**

The Examiner has rejected claims 28-30, alleging that a chemical name or structural formula is required in addition to the term "group B streptogramin derivative." (Office Action dated June 12, 2002, page 12, lines 19-21.) Applicants respectfully traverse this rejection for at least the reasons of record and the following reasons.

The Examiner fails to provide any reasoning for requiring such an amendment. Additionally, the Examiner has failed to at least consider the specification, wherein, for example, a detailed disclosure of group B streptogramins is provided. (Specification,

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page 8, line 20 through page 11, line 15.) Applicants respectfully submit that it is known in the art what is meant by the term group B streptogramin derivative. Please see, for example, U.S. Patent Nos. 4,618,599, 4,798,827, and 5,326,782 and European Patent Nos. 772,630 and 770,132. Because one of skill in the art can determine the scope of the claims from the specification and what is available to the public, the definiteness requirement is satisfied. Respectfully, Applicants request this rejection be withdrawn.

D. Claim 32

The Examiner suggests that claim 32 be amended to mandate the presence of the diluent or adjuvant to distinguish the composition from the compound. (Office Action dated June 12, 2002, page 13, lines 2-4.) Applicants have amended the claim in accordance with the Examiner's suggestion. Accordingly, Applicants respectfully request withdrawal of this rejection.

E. Claims 32 and 33

The Examiner questions "what is meant by the term 'pharmaceutical composition'." (Office Action dated June 12, 2002, page 13, lines 8-9.) As Applicants have amended the claim in accordance with the Examiner's suggestion, they respectfully request withdrawal of this rejection.

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IV. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: September 16, 2002

By: _____
Michele L. Mayberry
Reg. No. 45,644

Attachments: Appendix to Amendment

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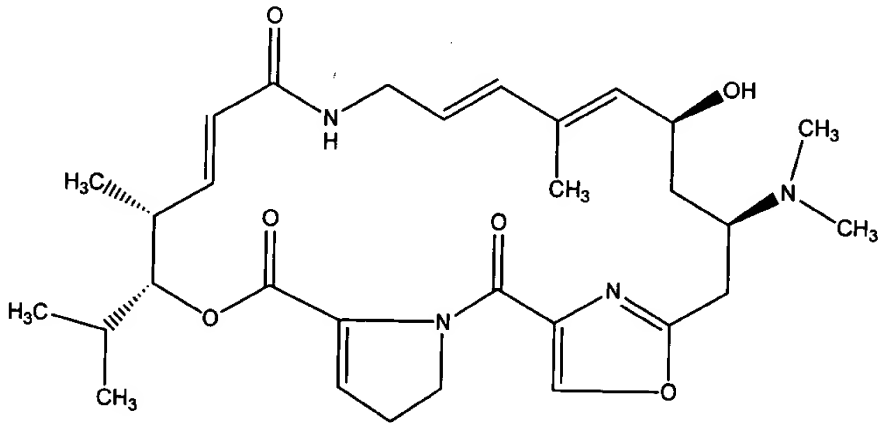
VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please replace claims 20-26, 32, and 33 with amended claims 20-26, 32, and 33, and please add new claims 34 and 35, as follows,:

20. (Once Amended) A group A streptogramin derivative according to claim 17, wherein said group A streptogramin is (16R)-16-dimethylamino-16-deoxopristinamycin II_A or a salt thereof:



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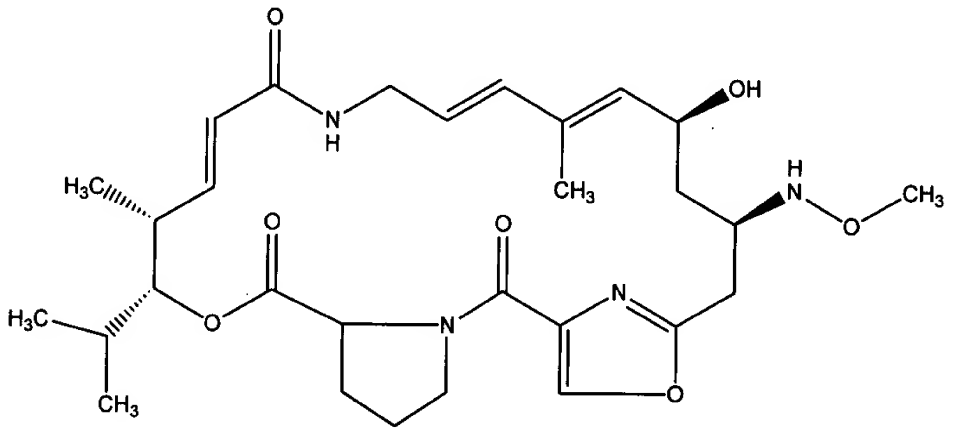
21. (Once Amended) A group A streptogramin derivative according to claim 17, wherein said group A streptogramin is (16R)-16-methoxyamino-16-deoxopristinamycin II_B or a salt thereof:



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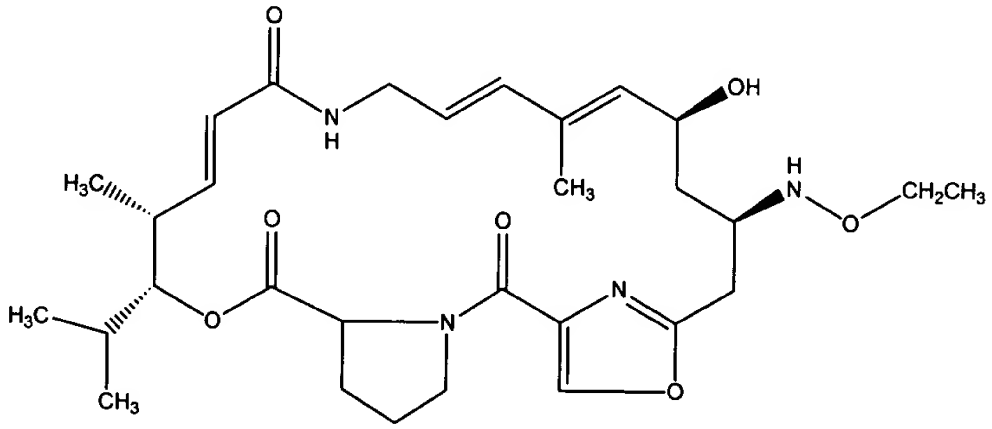
22. (Once Amended) A group A streptogramin derivative according to claim 17, wherein said group A streptogramin is (16R)-16-ethoxyamino-16-deoxopristinamycin II_B or a salt thereof:



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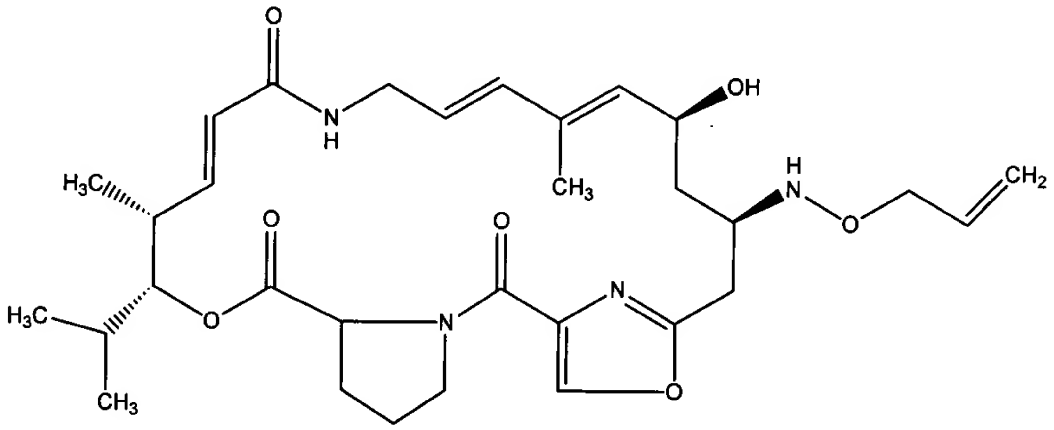
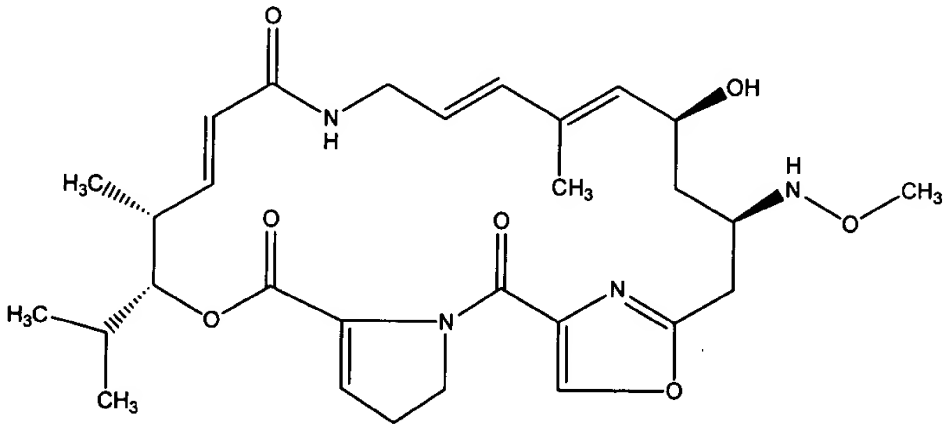
23. (Once Amended) A group A streptogramin derivative according to claim 17, wherein said group A streptogramin is (16R)-16-allyloxyamino-16-deoxopristinamycin II_B or a salt thereof:



24. (Once Amended) A group A streptogramin derivative according to claim 17, wherein said group A streptogramin is (16R)-16-methoxyamino-16-deoxopristinamycin II_A or a salt thereof:



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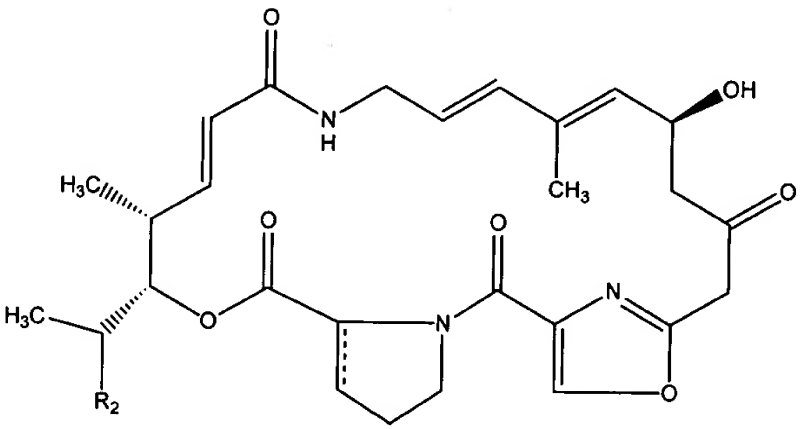
25. (Twice Amended) A process for preparing a group A streptogramin derivative according to claim 17, said process comprising:

(a) preparing a group A streptogramin derivative, wherein R' is a hydrogen atom, by reacting **for a time and under conditions to form a group A streptogramin according to claim 17**, in the presence of a reducing agent, an amine of formula (III):

H_2N-R" (III)

wherein R" is defined as in claim 17

with a natural pristinamycin of formula (II):



(II)

wherein R_2 is defined as in claim 17,

(b) optionally reacting said group A streptogramin derivative of formula (I), wherein R' is a hydrogen atom, with formaldehyde or a formaldehyde derivative to generate formaldehyde in situ **for a time and und r conditions** to form a second intermediate compound, and then reacting said second intermediate

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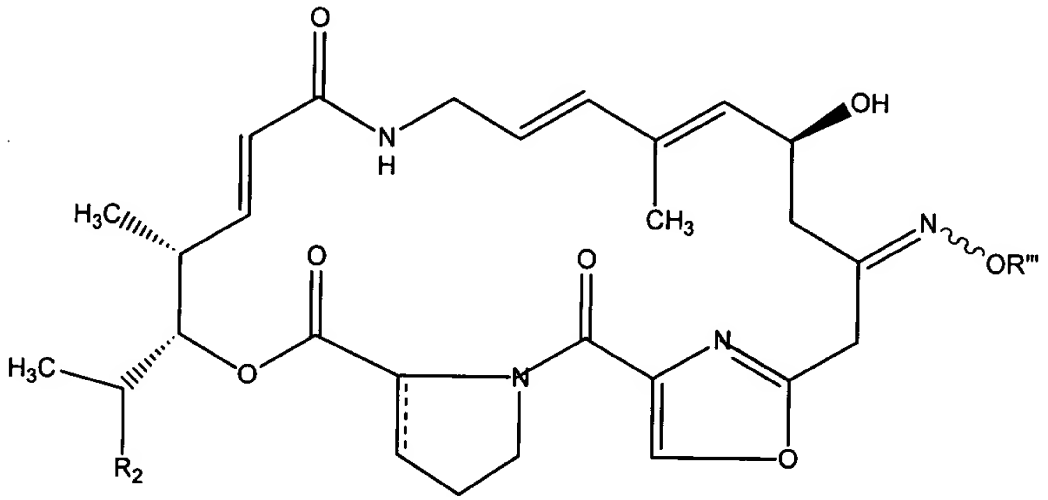
compound with a reducing agent **for a time and under conditions** to form a group A streptogramin derivative, wherein R' is a methyl group, and

(c) optionally converting said group A streptogramin derivative of formula (I), prepared by (a) or (b) above, to a salt and separating said salt, wherein the carbon bearing said R_1 is of the R configuration, or optionally separating said group A streptogramin derivative, wherein the carbon bearing said R_1 is of the R configuration.

26. (Once Amended) A process for preparing a group A streptogramin derivative according to claim 17, said process comprising:

(a) preparing an intermediate compound of formula (IV):



(IV)

wherein R_2 and R''' are defined as in claim 17

by reacting an amine of formula (III):

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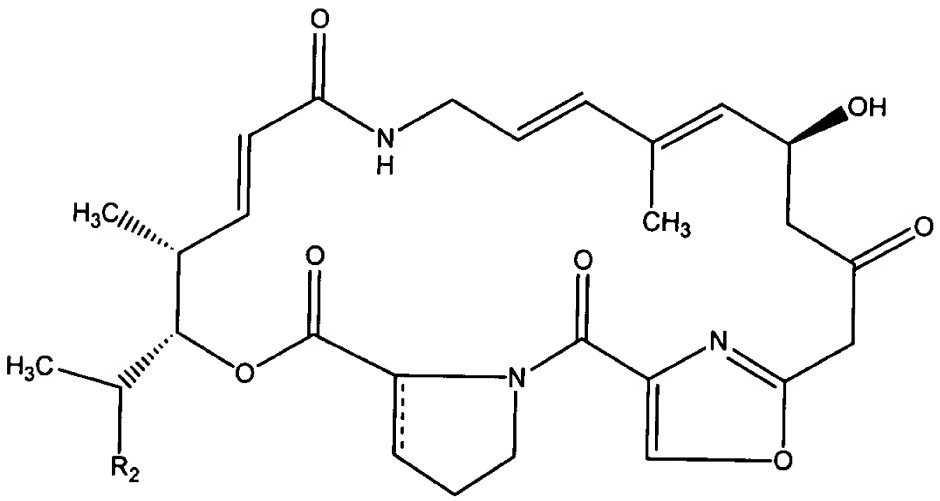
H_2N-R" (III)

wherein R" is chosen from –OR"' groups, and wherein said R"' groups are defined as in claim 17

with a natural pristinamycin of formula (II):



(II)

wherein R_2 is defined as in claim 17,

for a time and under conditions to form said intermediate compound of formula (IV),

(b) isolating said intermediate compound of formula (IV),

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(c) reacting said isolated intermediate compound of formula (IV) with a reducing agent **for a time and under conditions to form** ~~to prepare~~ a group A streptogramin derivative of formula (I), wherein R' is a hydrogen atom,

(d) optionally reacting said group A streptogramin derivative of formula (I), wherein R' is a hydrogen atom, with formaldehyde or a formaldehyde derivative capable of generating formaldehyde in situ **for a time and under conditions** to form a second intermediate compound, and then reacting said second intermediate compound with a reducing agent **for a time and under conditions** to form a group A streptogramin derivative of formula (I), wherein R' is a methyl group, and

(e) optionally converting said group A streptogramin derivative of formula (I), prepared by (c) or (d) above, to a salt and/or separating its R-epimer.

32. (Once Amended) A ~~pharmaceutical~~ composition comprising at least one group A streptogramin derivative of formula (I) or salt thereof according to claim 17, wherein said composition ~~optionally comprises at least one agent chosen from pharmaceutically acceptable diluents and pharmaceutically acceptable adjuvants~~ **comprises at least one pharmaceutically acceptable diluent, at least one pharmaceutically acceptable adjuvant, or at least one pharmaceutically acceptabl diluent and at l ast on pharmaceutically acceptable adjuvant**.

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33. (Once Amended) A ~~pharmaceutical~~ composition comprising at least one group A streptogramin derivative of formula (I) or salt thereof according to claim 17 and at least one group B streptogramin derivative, wherein said composition optionally comprises ~~at least one agent chosen from pharmaceutically acceptable diluents and pharmaceutically acceptable adjuvants~~ **at least one pharmaceutically acceptable diluent, at least one pharmaceutically acceptable adjuvant, or at l ast one pharmaceutically acceptable diluent and at least one pharmaceutically acceptable adjuvant**.

34. (New) A process for preparing a group A streptogramin derivative according to claim 17, said process comprising:

(a) preparing a group A streptogramin derivative, wherein R' is a hydrogen atom, by reacting for a time and under conditions to form a group A streptogramin according to claim 17, in the presence of a reducing agent, an amine of formula (III):

H_2N-R" (III)

wherein R" is defined as in claim 17

with a natural pristinamycin of formula (II):

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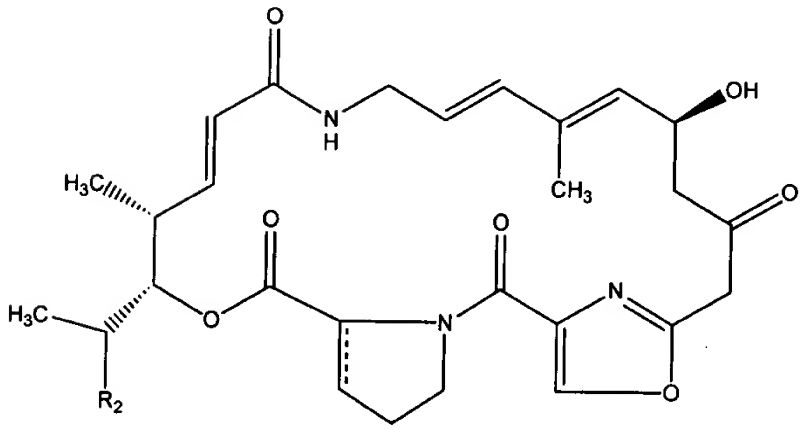

(II)

wherein R_2 is defined as in claim 17,

(b) optionally reacting said group A streptogramin derivative of formula (I), wherein R' is a hydrogen atom, with formaldehyde or a formaldehyde derivative to generate formaldehyde in situ for a time and under conditions to form a second intermediate compound, and then reacting said second intermediate compound with a reducing agent for a time and under conditions to form a group A streptogramin derivative, wherein R' is a methyl group,

(c) optionally converting said group A streptogramin derivative of formula (I), prepared by (a) or (b) above, to a salt and separating said salt, wherein the carbon bearing said R_1 is of the R configuration, or optionally separating said group A streptogramin derivative, wherein the carbon bearing said R_1 is of the R configuration, and

(d) isolating said group A streptogramin derivative of formula (I) or salt thereof, prepared by (a), (b), or (c) above.

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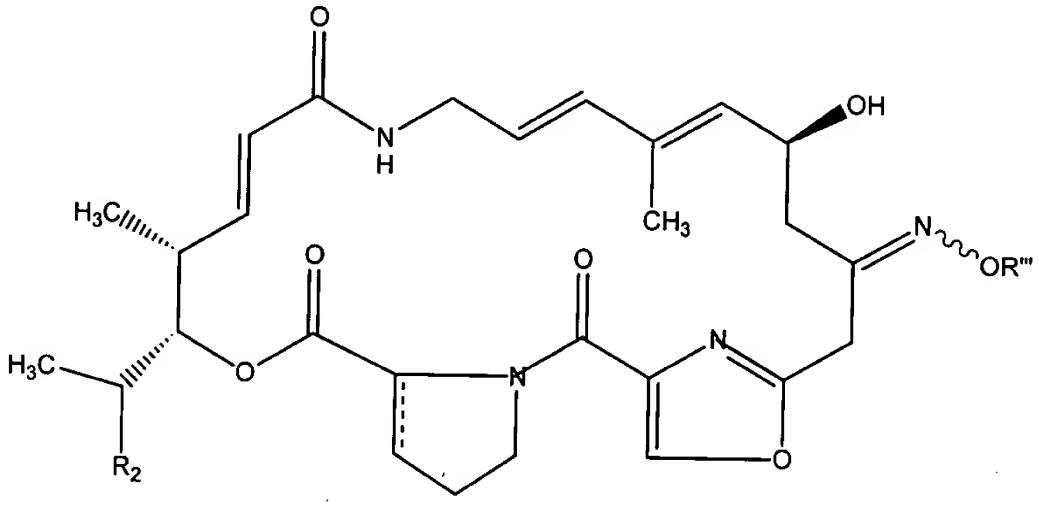
35. (New) A process for preparing a group A streptogramin derivative according to claim 17, said process comprising:

(a) preparing an intermediate compound of formula (IV):



(IV)

wherein R_2 and R''' are defined as in claim 17

by reacting an amine of formula (III):

H_2N-R'' (III)

wherein R'' is chosen from –OR''' groups, and wherein said R''' groups are defined as in claim 17

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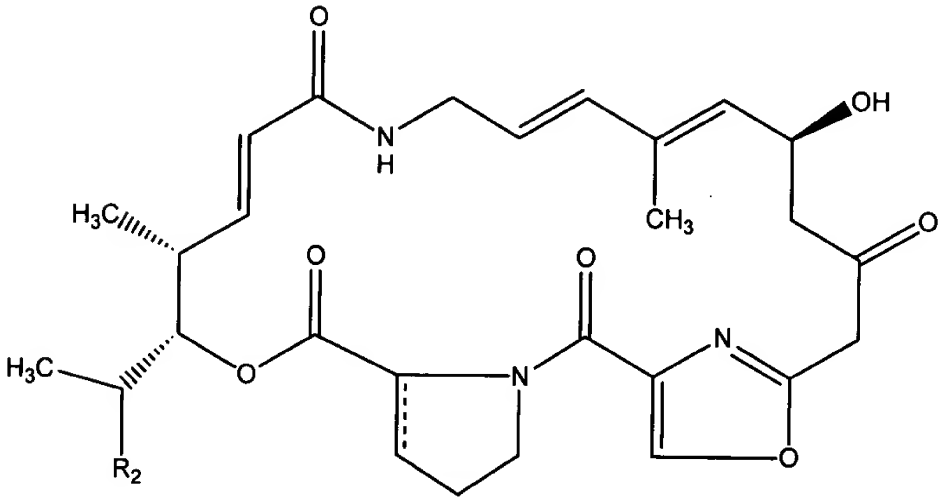
with a natural pristinamycin of formula (II):



(II)

wherein R_2 is defined as in claim 17,

for a time and under conditions to form said intermediate compound of formula (IV),

(b) isolating said intermediate compound of formula (IV),

(c) reacting said isolated intermediate compound of formula (IV) with a reducing agent for a time and under conditions to form a group A streptogramin derivative of formula (I), wherein R' is a hydrogen atom,

(d) optionally reacting said group A streptogramin derivative of formula (I), wherein R' is a hydrogen atom, with formaldehyde or a formaldehyde derivative capable

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of generating formaldehyde in situ for a time and under conditions to form a second intermediate compound, and then reacting said second intermediate compound with a reducing agent for a time and under conditions to form a group A streptogramin derivative of formula (I), wherein R' is a methyl group,

(e) optionally converting said group A streptogramin derivative of formula (I), prepared by (c) or (d) above, to a salt and/or separating its R-epimer, and

(f) isolating said group A streptogramin derivative of formula (I) or salt thereof, prepared by (c), (d), or (e) above.

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